REMARKS

Status of Claims and Amendment

Claims 5 and 6 have been amended. Claims 8, 10-14, 23-30, and 39-94 were previously canceled. Claims 1-7, 9, 15-22 and 31-38 are all the pending claims in the application. Claims 1-4, 9, 15-22 and 31-38 are withdrawn from consideration. Claims 5-7 are rejected.

Claims 5 and 6 have been amended to further clarify a "chrondrocye cell line derived from a Runx2/Cbfa1-". Support for the amendments to claims 5 and 6 may be found throughout the specification, for instance, at page 8, lines 23-26, page 9, 1st sentence of last full paragraph, page 10, lines 1-3, Figs 1-6, 9, 10, 11, page 24, lines 2-4, and Example 1.

The specification at pages 8-9, 24, 32-33, 62, and 68-69 have been amended to correct clerical and/or typographical errors in response to the objections to the specification.

In addition, the specification at page 13, line 23 has been amended to include a paragraph regarding the color drawings in compliance with 37 C.F.R. 1.84(a)(2)(iii) and in response to the Office Communication mailed February 12, 2009 denying Applicants' Petition for Acceptance of Color Drawings.

The Abstract has been amended to be in a single paragraph and within 150 words in response to the objections to the specification. In addition, the word "means" has been replaced with "method". Applicants note that it would have been apparent to one of ordinary skill from reading the specification, for instance at page 9, lines 8-10, that other methods may be used to screen for the induction or inhibition of gene expression.

No new matter is added.

Claim to Priority

Applicants thank the Examiner for acknowledging Applicant's claim to priority of JP 2003-359172 filed October 20, 2003 , as well as receipt of a certified copy of the priority document.

Information Disclosure Statements

Applicants thank the Examiner for acknowledging the Information Disclosure Statements filed April 20, 2006 and May 6, 2008, by returning signed and initialed copies of the PTO Forms SB/08 submitted therewith.

Applicants respectfully request that the Examiner acknowledge the Information Disclosure Statements submitted March 19, 2009 and May 21, 2009, and the references cited therein.

Drawings and Response to Office Communication Denying of Applicants' Petition for Acceptance of Color Drawings mailed February 12, 2009

Applicants thank the Examiner for indicating on the Office Action Summary sheet, acceptance of the Drawings filed April 20, 2006.

However, in the Office Communication issued February 12, 2009, Applicants' Petition for Acceptance of Color Drawings is denied. Specifically, the Examiner notes that the specification does not meet the requirements of 37 C.F.R. § 1.84(a)(2)(iii) for incorporation of color drawings under 37 C.F.R. § 1.84(a)(2)(iv). Accordingly, the specification has been amended herewith to contain the appropriate language in accordance with 37 C.F.R. § 1.84(a)(2)(iii).

Further, the Examiner requests an explanation of why the color drawings are necessary. Applicants note that Figures 1 and 15-34 are submitted in color for the following reasons. Figure

1 is an optical phase-contrast microscope photograph to show the morphologies of the claimed Runx2/Cbfa1- and p53-deficient cell lines and the claimed Runx2/Cbfa1-deficient mouse-derived chondrocyte cell line. Figures 15-19 are photograph images of HE-stained sections to show cartilage differentiation and expression analysis via *in situ* hybridization, Figures 20-24 are photographs of HE-stained HCK transgenic mouse showing the stained skeleton, Figures 25-28 are photograph images of HE- and Kossa-stained tibia of GALNT3 transgenic mouse and expression analysis via *in situ* hybridization, Figure 29 is a photograph showing results of *in situ* hybridization expression analysis of aggrecan in the tibia of GALNT3 transgenic mouse, Figure 30 is a photograph showing the results of safranin O staining of the tibia of GALNT3 mouse Figure 31 is a photograph showing the results of PAS staining of the anklebone of GALNT3 mouse, Figure 32 is a photograph showing immunostained fibronectin in the tibia of GALNT3 transgenic mouse elopment, Figure 33 is a photograph showing the results of Brdu labeling, and Figure 34 is a photograph showing the results of Tunnel staining for apoptosis in the tibia of GALNT3 mouse. Thus, the color photographs submitted for the present application are a necessary and practical medium to best convey the results of various staining tests performed and disclose the claimed subject matter.

Applicants respectfully request reconsideration and acceptance of the color drawings filed April 20, 2006.[1]

[1] Applicants note that three copies of the photographs for Figure 1 and Figures 15 through 34 were previously submitted, and the specification has been amended as discussed above to be in compliance with 37 C.F.R. § 1.84(a)(2)(iii) for incorporation of color drawings under 37 C.F.R. § 1.84(a)(2).

Response to Objections to the Specification

1. The Examiner objects to the Abstract because the Abstract contains more than 150 words and includes legal phraseology, such as "means".

In response, and solely to advance prosecution of the present application, Applicants have amended the specification as suggested by the Examiner, and removed the term "means" from the Abstract.

Withdrawal of the grounds of objection is respectfully requested.

2. The Examiner objects to the specification because the disclosure contains the following informalities:

(a) the term "Runx2/Cbfa1" is misspelled as "Runx2/Cba1" (paragraph bridging pages 8-9; page 32, last full paragraph; paragraph bridging pages 32-33); and

(b) the trademarks GENBANK (page 24, 2nd paragraph), ISOGEN (page 62, Example 1, section (4); page 68, Example 4, section (1); page 69, Example 4, section (2)), OLIGOTEX (page 68, Example 4, section (1)), and LIFEARRAY (page 68, Example 4, section (1)) should be capitalized wherever they appear and be accompanied by the generic terminology.

In response, and solely to advance prosecution of the present application, Applicants have amended the specification to correct typographical errors, and to capitalize and indicate the trademarks.

Withdrawal of the grounds of objection is respectfully requested.

Response to Claim Rejection Under 35 U.S.C. § 112

Claim 7 is rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement.

The Office Action asserts that it is unclear whether the claimed RU-1 and Ru-22 cell lines derived from a Runx2/Cbfa1- and p53-deficient mouse, which meet the requirements for a biological material set forth in 37 C.F.R. § 1.801, are obtainable by a reproducible method or is known and readily available to the public pursuant to 37 C.F.R. §§ 1.801 through 1.809. At pages 5-6, the Office Action sets forth reasons to support the contention that the guidance provided in the specification is insufficient to enable one of ordinary skill in the art to make the claimed RU-1 and RU-22 cell lines without undue experimentation.

Accordingly, the Office Action asserts that availability of the claimed biological material is necessary to satisfy the enablement provisions of 35 U.S.C. § 112, by providing a statement of assurance in compliance with 37 C.F.R. §§ 1.801-1.809 that the FERM-BP-10137 and FERM BP-10138 deposits made at the International Patent Organism Depositary of the National Institute of Advanced Industrial Science and Technology under the Budapest Treaty, are obtainable or available and that all restrictions on the availability to the public of the material so deposited will be irrevocably removed upon granting of a patent.

The Office Action acknowledges that the specification contains the deposit accession numbers, date of deposit, name and address of the depository, and a description of the deposited material.

In response, and solely to advance prosecution of the present application, Applicants submit herewith a Statement of Availability for both FERM-BP-10137 and FERM BP-10138.

Withdrawal of the rejection under § 112, first paragraph, is respectfully requested.

Rejection of Claims Under 35 U.S.C. § 102

Claim 5 is rejected under 35 U.S.C. § 102(b) as being anticipated by Kobayashi *et al.* (Biochemical and Biophysical Research Communications, 273: 630-636 (2000)).

Kobayashi is asserted by the Office Action to allegedly teach a Runx2/Cbfa1 deficient mouse-derived primary chondrocyte cell culture.

In response, Applicants note that the presently claimed chondrocyte cell line derived from a Runx2/Cbfa1-deficient mouse is neither explicitly or implicitly disclosed by Kobayashi.

The Office Action has failed to establish a *prima facie* case of anticipation which requires that all words in a claim must be considered in judging the patentability of that claim against the prior art, i.e., each and every limitation as set forth in the claim must be found in a single prior art reference. M.P.E.P. §2131 and §2143.03. Kobayashi does not teach chondrocytes which are derived from a mouse that is Runx2/Cbfal-deficient.

The present cell line maintains morphology or phenotype of a chondrocyte in spite of the deficiency of Runx2/Cbfa1 (page 62, lines 4-8, and page 63, lines 2-11 of the specification). In this regard, Enomoto et al. (J. Cell Science, 117(3): 417-425 (2004)[1], published after the priority date of the present application, discloses that chondrocytes isolated from Runx2-deficient mice gradually accumulate lipid droplets, show increased expression of adipocyte-related differentiation marker genes and decreased expression of type II collagen. Enomoto concluded that the depletion of Runx2 resulted in the loss of the differentiated phenotype in chondrocytes and induced adipogenic differentiation, so that Runx2 plays an important role in maintaining the chondrocyte phenotype (Summary).

[1] In accordance with M.P.E.P. § 609.05(c), the documents cited herein in support of Applicants' remarks are being submitted as evidence directed to an issue raised in the Official Action, and no fee pursuant to 37 C.F.R. 1.97 or 1.98, or citation on a FORM PTO/SB/08A & B is believed to be necessary.

In contrast, Kobayashi discloses that calvaria cells are obtained from Cbfa1-deficient mice, and the cells differentiate into chondrocytes. The calvaria cells derived from Cbfa1-deficient mice described in Kobayashi contain numerous adipocyte foci, and the cells differentiate into chondrocytes and then to terminal hypertrophic chondrocytes (see Summary). Thus, Kobayashi fails to obtain or disclose a homogenous cell line which stably shows phenotypes of chondrocytes.

Furthermore, based on the disclosure of Kobayashi as evidenced by Enomoto, one of ordinary skill in the art at the time the invention was made would not have expected to obtain a homogenous chondrocyte cell line from Runx2-deficient mouse, which maintains the phenotype of a chondrocyte in spite of the deficiency of Runx2.

The present inventors are the first to succeed in establishing a chondrocyte cell line which is deficient in Runx2/Cbfal but surprisingly maintains the chondrocyte morphology or phenotype. These results are surprising and unexpected in view of the technical knowledge and understanding available in the art at the time the invention was made, as evidenced by Enomoto.

Thus, the chondrocyte cell line of claim 5 is neither anticipated by nor rendered obvious by Kobayashi.

Reconsideration and withdrawal of the rejection under § 102(b) is respectfully requested.

Response to Claim Rejection Under 35 U.S.C. § 103

Claim 6 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Kobayashi in view Kamiya (Journal of Bone and Mineral Research, 17(10): 1832-1842 (2002)).

Kobayashi appears to be asserted for the same reasons discussed above, i.e., for teaching a Runx2/Cbfal deficient mouse-derived primary chondrocyte cell culture.

The Office Action admits that Kobayashi does not teach chondrocytes which are derived from a mouse that is p53 deficient and Runx2/Cbfal-deficient.

Kamiya is asserted for teaching a p53-null mouse and the derivation of chondrocytic cells and chondrocytes from the p53-null mouse. Kamiya is asserted to teach that the chondrocytic cell line derived from the p53-null mouse is capable of reproducing the whole process of chondrocyte differentiation, and providing an excellent model to study cartilage development, homeostasis and function. Further, the Office Action asserts that Kamiya teaches p53-deficiency is sufficient to establish immortalized cell lines because p53 is not present to inhibit proliferation.

Thus, the Office Action concludes that it would have been obvious to one of ordinary skill in the art at the time the invention was made to obtain the claimed chondrocyte derived from a Runx2/Cbfal-and p53-deficient mouse by mating the Runx2/Cbfa mouse line of Kobayashi with the p53 mouse line of Kamiya, isolating chondrocytic cells from the bone at E18.5, and subjecting the cells to culture conditions to promote the differentiation of the cells to chondrocytes. The Office Action appears to assert that the motivation and reasonable expectation of success of making such a modification is gleaned from the expected benefit of providing chondrocytes that are also deficient in p53, resulting in increased proliferation and immortalization in culture, while retaining the ability to differentiate to chondrocytes, as taught by Kamiya.

In response, Applicants note that the Office Action has failed to establish a *prima facie* case of obviousness for at least the following reasons.

First, Applicants note that for the same reasons as discussed above, Kobayashi does not teach or suggest the presently claimed chondrocyte cell line which is deficient in Runx2/Cbfal-

but maintains the chondrocyte morphology or phenotype. Further, as admitted by the Office Action, Kobayashi does not teach or suggest chondrocytes which are derived from a mouse that is p53 deficient and Runx2/Cbfal-deficient. In addition, as evidenced by Enomoto, the calvaria cells derived from Cbfa1-deficient mice described in Kobayashi contain numerous adipocyte foci, and the cells differentiated into chondrocytes and further to terminal hypertrophic chondrocytes. Thus, Kobayashi fails to teach or suggest a homogenous cell line which stably shows phenotypes of chondrocytes.

Kamiya does not cure the deficiency of Kobayashi because Kamiya only teaches a specific clonal chondrocytic cell line N1511 derived from rib cartilage of a p53-null mouse. The combination of Kobayashi and Kamiya do not teach or suggest all of the claim limitations, i.e., the claimed chondrocyte cell line derived from mouse having both Runx2/Cbfa1- and p53-deficiency. M.P.E.P. § 2143.

Second, as discussed above, since one of ordinary skill in the art would not have expected to obtain the claimed chondrocyte cell line from Runx2/Cbfa1-deficient mouse, which maintains morphology or phenotype of chondrocyte, there would have been less expectation to obtain a stable chondrocyte cell line from a mouse which is both Runx2/Cbfa1-deficient and p53-deficient even in view of Kamiya. At the time the invention was made, it was thought that chondrocytes isolated from Runx2/Cbfa1-deficient mouse contained adipocytes as disclosed in Kobayashi and evidenced by Enomoto.

Accordingly, one of ordinary skill in the art would have expected that chondrocytes isolated from Runx2/Cbfa1- and p53-deficient mouse would also contain heterologous cells. Thus, one of ordinary skill in the art would not have been motivated or had a reasonable

expectation of success of obtaining a chondrocyte cell line from Runx2/Cbfa1- and p53-deficient mouse, as presently claimed.

To the contrary, the chondrocyte cell line of claim 6 are homogenous cells and maintain the morphology or phenotype of undifferentiated chondrocytes despite the Runx2/Cbfa1-deficiency. Because of these features, the claimed chondrocyte cell line may be used to observe the differentiation of permanent cartilage into growth cartilages as well as screen for a gene essential for cartilage differentiation when Runx2/Cbfa1 gene is expressed in the chondrocyte cell line. Further, as discussed above, the chondrocytes derived from Runx2/Cbfa1-deficient mouse disclosed in Kobayashi and as evidenced by Enomoto, cannot be used for observing chondrocyte differentiation, because the chondrocytes contain adipocytes, which are not stable and may differentiate during culture. As disclosed at the paragraph bridging page 634 to page 635 of Kobayashi, because the Cbfa1-deficient calvarial cells contain adipocytes, the cells differentiated in culture to multi-potential mesenchymal cells.

Third, even if *arguendo*, one of ordinary skill in the art was somehow motivated to modify Kobayashi with Kamiya in the manner asserted by the Office Action, one of ordinary skill in the art would not have obtained the presently claimed chondrocyte cell line derived from a Runx2/Cbfa1- and p53-deficient mouse for at least the reasons discussed above.

Reconsideration and withdrawal of the rejection under § 103(a) is respectfully requested.

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

/Tu A. Phan/

Tu A. Phan, Ph.D.
Registration No. 59,392

SUGHRUE MION, PLLC
Telephone: (202) 293-7060
Facsimile: (202) 293-7860

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